General

Guideline Title

EFNS-ENS guidelines for the use of PCR technology for the diagnosis of infections of the nervous system.

Bibliographic Source(s)

Steiner I, Schmutzhard E, Sellner J, Chaudhuri A, Kennedy PG. EFNS-ENS guidelines for the use of PCR technology for the diagnosis of infections of the nervous system. Eur J Neurol. 2012 Oct;19(10):1278-91. [181 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Viruses

Table. Recommendations for the Use of Polymerase Chain Reaction (PCR) for the Diagnosis of Central Nervous System (CNS) Viral Infections

Virus	Reported Sensitivity and Specificity of Cerebrospinal Fluid (CSF) PCR	Evidence Class and Level of Recommendation
Herpes simplex virus (HSV)-1 Encephalitis	96% and 99% (Tebas, Nease, & Storch, 1998)	Class 1 Level A May be false negatives during first 3 days
Varicella-Zoster virus (VZV)	80% and 98% (Corral et al., 2003)	Class III Level C CSF anti-VZV IgG more sensitive than PCR in VZV vasculopathy
Cytomegalovirus (CMV)	92% and 94% (Gozlan et al., 1995)	Class II Level B Quantitative PCR may also be clinically useful
Epstein–Barr Virus (EBV)	97%–100% and 98.5% (d'Arminio Montforte et al., 1997; Cinque et al., 1993; Cinque et al., 1996)	Class IV Level C Quantitative PCR may also be clinically useful
Enteroviruses	31%–95% and 92%–100% (Romero, 1999; DeBiasi & Taylor, 1999; Pérez-Vélez et al., 2007)	Class II Level B
JC virus (JCV)	50%–82% and 98.5%–100% (Weber et al., 1994; Weber	Class II Level B

Virus	Reported Sensitivity and Specificity of Cerebrospinal Fluid (CSF) PCR	Evidence Class and Level of Recommendation
Human immunodeficiency virus (HIV)	et al., 1997; Hirsch et al., 1998) Diagnosis will already have been made on the blood	Quantitative PCR may also be clinically useful CSF viral load useful tool in assessing neurological involvement
Human T-cell lymphotropic Virus (HTLV-1)	75%–99.4% and 98.5% (DeBiasi & Taylor, 1999; Andrade et al., 2010)	Class III Level C Combination of CSF PCR and anti-HTLV-1 antibody index useful in diagnosis

Abbreviations: CSF, cerebrospinal fluid; IgG, immunoglobulin G; JC, John Cunningham; PCR, polymerase chain reaction

Bacteria

Acute Meningitis

For reasons of high inter-assay variability and low specificity, in house nucleic acid amplification methods for diagnosis of bacterial infections in cerebrospinal fluid (CSF) are deemed unreliable and should not be used in clinical practice (Class IV Grade C). The robustness of various commercial polymerase chain reaction (PCR) tools that are currently available and the choice of uniplex or multiplex quantitative reverse transcription (RT)-PCR for appropriate levels of diagnostic specificity and sensitivity are presently unclear and remain to be defined by field tests and comparative studies (Class IV Grade C).

Chronic Meningitis

The diagnostic yield of PCR in CSF is influenced by the time to test after initiation of antibiotic therapy. Repeating CSF PCR within first 3 weeks may aid diagnosis in tuberculous meningitis if the initial result is negative (Class IV, Grade C). CSF-PCR is not presently a validated diagnostic test for Lyme neuroborreliosis (Class IV, Grade C).

Summary of Recommendations for Bacteria

Commercially available and standardized quantitative RT-PCR is a valuable adjunct for diagnosis of bacterial meningitis and is recommended for routine use in CSF samples (Class II, Grade A) of patients with suspected bacterial meningitis. However, direct microscopy and culture remain the gold standard of microbiological diagnosis of bacterial infections of central nervous system where feasible and current range of diagnostic bacterial PCR tests do not replace them (Class II Grade A).

Parasites

Microscopy and serology show many limitations in the diagnosis of protozoal infections or helminthic infestations of the CNS. Molecular techniques have enabled parasitologists and neuroinfectiologists to use the gene amplification methods to establish the diagnosis from any kind of body fluids, that is, also the CSF, or biopsy material. Conventional PCR has been supplemented by nested and multiplex PCR as well as real-time PCR for the detection of several parasitic infestations and infections, respectively. Recently, even more modern techniques as loop-mediated isothermal amplification (LAMP) and luminex-based assays have been proposed as possible diagnostic techniques in parasitic diseases of the nervous system. As these techniques allow the detection of infestations or infections from samples with very low burden of parasites, these molecular-based approaches offer higher sensitivity and enhanced specificity compared with existing diagnostic tests. These techniques have been established, at least in part, as the reference diagnostic tool in European laboratories, and they are used for research purposes in tropical areas. However, they are far from having become daily routine in the diagnosis of parasitic infections and infestations of the CNS in resource-poor countries where history, clinical signs and symptoms, and direct light microscopy still remain the mainstay of diagnosing CNS parasitoses.

Fungal Infections

The use and ability to provide diagnosis of neurological infection by PCR varies according to the group of pathogens. No doubt: the main contribution of this technology is to the diagnosis of infections caused by viruses followed by bacterial infections of the CNS with the notable exception of tuberculous meningitis.

The efficacy of this tool for the diagnosis of both protozoal infections and helminthic infestations has also been established in many instances. Unfortunately, the molecular technology at large, including PCR, is far from becoming routine in resource-poor countries where such infections are prevalent.

As for fungal infections, despite their importance in the context of the immune-compromised host, there is not enough data to recommend the routine use of PCR. More clinical research is required to test and eventually confirm its role in this group of infections.

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation.

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls).

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Infections of the nervous system, including viral, bacterial, and parasitic infections

Guideline Category

Diagnosis

Clinical Specialty

Family Practice

Infectious Diseases

Internal Medicine

Neurology

Pediatrics

Intended Users

Clinical Laboratory Personnel

Physician Assistants

Physicians

Guideline Objective(s)

To guide neurologists and infectious diseases experts in the application of polymerase chain reaction technology to the diagnosis of infections of the nervous system

Target Population

Patients who have or are suspected to have a viral, bacterial, or parasitic infection of the nervous system

Interventions and Practices Considered

1. Polymerase chain reaction (PCR)
2. Real-time PCR
3. Nested and semi-nested PCR
4. Multiplex PCR
5. High throughput multiplex PCR
6. Probe-based detection with luminex beads
7. Reverse transcription (RT)-PCR
8. Quantitative nucleic acid sequence-based amplification
9. Loop-mediated isothermal amplification (LAMP)
10. PCR enzyme-linked immunosorbent assay (ELISA)
11. Nucleic acid sequence-based amplification and PCR coupled to oligo-chromatography
12. Microscopy and culture

Note: The following were considered but not recommended: in house nucleic acid amplification methods for diagnosis of bacterial infections in cerebrospinal fluid (CSF) in clinical settings; CSF-PCR for Lyme neuroborreliosis, routine use of PCR for diagnosis of fungal infections.

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests for nervous system infections
- Positive and negative predictive values of the diagnostic tests
- Usability of diagnostic tests in resource poor countries

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The Task Force searched MEDLINE (National Library of Medicine) for relevant literature from 1966 to July 2011. The search included reports of research in human beings only and in English. The Cochrane library and the guideline section of the American Academy of Neurology were assessed on July 15th, 2011. Review articles and book chapters were also included if they were considered to provide comprehensive reviews of the topic. The final choice of literature and the references included was based on judgment of the Task Force on the relevance to this subject. The final literature search was performed in May 2012.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation.

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls).

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Recommendations were reached by consensus of all Task Force participants and were also based on their awareness and clinical experience.

Rating Scheme for the Strength of the Recommendations

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see the "Availability of Companion Documents" field).

Evidence Supporting the Recommendations

References Supporting the Recommendations

Andrade RG, Ribeiro MA, Namen-Lopes MS, Silva SM, Basques FV, Ribas JG, Carneiro-Proietti AB, Martins ML. Evaluation of the use of real-time PCR for human T cell lymphotropic virus 1 and 2 as a confirmatory test in screening for blood donors. Rev Soc Bras Med Trop. 2010 Mar-Apr;43(2):111-5. PubMed

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Corral I, Quereda C, Antela A, Pintado V, Casado JL, Martin-Davila P, Navas E, Moreno S. Neurological complications of varicella-zoster virus in human immunodeficiency virus-infected patients: changes in prevalence and diagnostic utility of polymerase chain reaction in cerebrospinal fluid. J Neurovirol. 2003 Feb;9(1):129-35. PubMed

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DeBiasi RL, Tyler KL. Polymerase chain reaction in the diagnosis and management of central nervous system infections. Arch Neurol. 1999 Oct;56(10):1215-9. [17 references] PubMed

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Perez-Velez CM, Anderson MS, Robinson CC, McFarland EJ, Nix WA, Pallansch MA, Oberste MS, Glode MP. Outbreak of neurologic enterovirus type 71 disease: a diagnostic challenge. Clin Infect Dis. 2007 Oct 15;45(8):950-7. PubMed

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Tebas P, Nease RF, Storch GA. Use of the polymerase chain reaction in the diagnosis of herpes simplex encephalitis: a decision analysis model. Am J Med. 1998 Oct;105(4):287-95. PubMed

Weber T, Klapper PE, Cleator GM, Bodemer M, Luke W, Knowles W, Cinque P, Van Loon AM, Grandien M, Hammarin AL, Ciardi M, Bogdanovic G. Polymerase chain reaction for detection of JC virus DNA in cerebrospinal fluid: a quality control study. European Union Concerted Action on Viral Meningitis and Encephalitis. J Virol Methods. 1997 Dec;69(1-2):231-7. PubMed

Weber T, Turner RW, Frye S, Ruf B, Haas J, Schielke E, Pohle HD, Luke W, Luer W, Felgenhauer K, et al.. Specific diagnosis of progressive multifocal leukoencephalopathy by polymerase chain reaction. J Infect Dis. 1994 May;169(5):1138-41. PubMed

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of polymerase chain reaction (PCR) technology for the diagnosis of infections of the nervous system

Potential Harms

False-negative test results

Qualifying Statements

Qualifying Statements

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

Implementation of the Guideline

Description of Implementation Strategy

The European Federation of Neurological Societies (EFNS) has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

Implementation Tools

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Steiner I, Schmutzhard E, Sellner J, Chaudhuri A, Kennedy PG. EFNS-ENS guidelines for the use of PCR technology for the diagnosis of infections of the nervous system. Eur J Neurol. 2012 Oct;19(10):1278-91. [181 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Oct

Guideline Developer(s)

European Academy of Neurology - Medical Specialty Society

European Neurological Society - Medical Specialty Society

Source(s) of Funding

European Federation of Neurological Societies

Guideline Committee

European Federation of Neurological Societies (EFNS) Task Force on the Use of PCR Technology for the Diagnosis of Infections of the Nervous

System

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available to registered users from the European Federation of Neurological Societies Web site .

Availability of Companion Documents

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies (EFNS) Web site .
- Continuing Medical Education questions are available to registered users from the EFNS Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on November 20, 2012. The information was verified by the guideline developer on January 30, 2013.

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